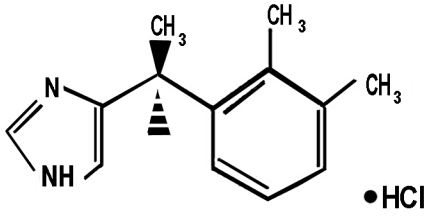
Precedex™
Dexmedetomidine Hydrochloride Injection

DESCRIPTION
Precedex™ (dexmedetomidine hydrochloride injection) is a sterile, nonpyrogenic solution suitable for intravenous infusion following dilution. Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Dexmedetomidine has a molecular weight of 236.7 and the empirical formula is C13H16N2 • HCl and the structural formula is:



Dexmedetomidine hydrochloride is a white or almost white powder that is freely soluble in water and has a pKa of 7.1. Its partition coefficient in-octanol: water at pH 7.4 is 2.89. Precedex is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7.0. Each 1 mL of Precedex contains 118 mcg of dexmedetomidine HCl (equivalent to 100 mcg dexmedetomidine base) and 9 mg of sodium chloride in water. The solution is preservative-free and contains no additives or chemical stabilizers.

CLINICAL PHARMACOLOGY
General:
Dexmedetomidine is a relatively selective alpha$_2$-adrenoceptor agonist with sedative properties. Alpha$_2$ selectivity is observed in animals following slow Intravenous (IV) infusion of low and medium doses (10-300 mcg/kg). Both alpha$_1$ and alpha$_2$ activity is observed following slow IV infusion of high doses ($\geq$1000 mcg/kg) or with rapid IV administration.

In a study in healthy volunteers (N=10), respiratory rate and oxygen saturation remained within normal limits and there was no evidence of respiratory depression when Precedex was administered by IVinfusion at doses within the recommended dose range (0.2 – 0.7 mcg/kg/hr).

Pharmacokinetics:
Following intravenous administration, dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life (t1/2) of approximately 6 minutes; a terminal elimination half-life ($t_{1/2}$) of approximately 2 hours; and steady-state volume of distribution (Vss) of approximately 118 liters. Clearance is estimated to be approximately 39 L/h. The mean body weight associated with this clearance estimate was 72 kg.

Dexmedetomidine exhibits linear kinetics in the dosage range of 0.2 to 0.7 µg/kg/hr when administered by IV infusion for up to 24 hours. Table 1 shows the main pharmacokinetic parameters when Precedex was infused (after appropriate loading doses) at maintenance infusion rates of 0.17 µg/kg/hr (target concentration of 0.3 ng/mL) for 12 and 24 hours, 0.33 µg/kg/hr (target concentration of 0.6 ng/mL) for 24 hours, and 0.70 µg/kg/hr (target concentration of 1.25 ng/mL) for 24 hours.

Table 1.	Mean ±SD Pharmacokinetic Parameters			
Parameter	**Loading Infusion (min)/Total infusion duration (hrs)**			
	10 min/12 hrs	**10 min/24 hrs**	**10 min/24 hrs**	**35 min/24 hrs**
	Dexmedetomidine Target Concentration (ng/mL) and Dose (mcg/kg/hr)			
	0.3/0.17	**0.3/0.17**	**0.6/0.33**	**1.25/0.70**
$t_{1/2}$*, hour	1.78 ±0.30	2.22 ±0.59	2.23 ±0.21	2.50 ±0.61
CL, liter/hour	46.3 ±8.3	43.1 ±6.5	35.3 ±6.8	36.5 ±7.5
Vss, liter	88.7±22.9	102.4±20.3	93.6 ±17.0	99.6±17.8
Avg Css #, ng/mL	0.27 ±0.05	0.27 ±0.05	0.67 ±0.10	1.37 ±0.20

* Presented as harmonic mean and pseudo standard deviation.
# Avg Css = Average steady-state concentration of dexmedetomidine. (2.5 – 9 hour samples for 12 hour infusion and 2.5 – 18 hour samples for 24 hour infusions).

Distribution

The steady-state volume of distribution (Vss) of dexmedetomidine is approximately 118 liters. Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female volunteers. The average protein binding was 94% and was constant across the different concentrations tested. Protein binding was similar in males and females. The fraction of dexmedetomidine that was bound to plasma proteins was statistically significantly decreased in subjects with hepatic impairment compared to healthy subjects.

The potential for protein binding displacement of dexmedetomidine by fentanyl, ketorolac, theophylline, digoxin and lidocaine was explored *in vitro*, and negligible changes in the plasma protein binding of dexmedetomidine were observed. The potential for protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin by dexmedetomidine was explored *in vitro* and none of these compounds appeared to be significantly displaced by dexmedetomidine.

Metabolism

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450 mediated metabolism. The major metabolic pathways of dexmedetomidine are: direct N-glucuronidation to inactive metabolites; aliphatic hydroxylation (mediated primarily by CYP2A6) of dexmedetomidine to generate 3-hydroxy dexmedetomidine, the glucuronide of 3-hydroxy dexmedetomidine, and 3-carboxy dexmedetomidine; and N-methylation of dexmedetomidine to generate 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N-methyl O-glucuronide dexmedetomidine.

Elimination

The terminal elimination half-life (t1/2) of dexmedetomidine is approximately 2 hours and clearance is estimated to be approximately 39 L/h. A mass balance study demonstrated that after nine days an average of 95% of the radioactivity, following IV administration of radiolabeled dexmedetomidine, was recovered in the urine and 4% in the feces. No unchanged dexmedetomidine was detected in the urine. Approximately 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion. Fractionation of the radioactivity excreted in urine demonstrated that products of N-glucoronidation accounted for approximately 34% of the cumulative urinary excretion. In addition, aliphatic hydroxylation of parent drug to form 3-hydroxy dexmedetomidine, the glucuronide of 3-hydroxy dexmedetomidine, and 3-carboxylic acid dexmedetomidine together represented approximately 14% of the dose in urine. N-methylation of dexmedetomidine to form 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N-methyl O-glucuronide dexmedetomidine accounted for approximately 18% of the dose in urine. The N-Methyl metabolite itself was a minor circulating component and was undetected in urine. Approximately 28% of the urinary metabolites have not been identified.

Gender:

There was no observed difference in dexmedetomidine pharmacokinetics due to gender.

Geriatrics:

The pharmacokinetic profile of dexmedetomidine was not altered by age. There were no differences in the pharmacokinetics of dexmedetomidine in young (18 – 40 years), middle age (41 – 65 years), and elderly (>65 years) subjects.

Pediatrics:

The pharmacokinetic profile of dexmedetomidine has not been studied in pediatric patients.

Renal Impairment:

Dexmedetomidine pharmacokinetics (Cmax, Tmax, AUC, t1/2, CL, and VSS) were not significantly different in subjects with severe renal impairment (creatinine clearance: <30 mL/min) compared to healthy subjects. However, the pharmacokinetics of the metabolites of dexmedetomidine have not been evaluated in patients with impaired renal function. Since the majority of metabolites are excreted in the urine, it is possible that the metabolites may accumulate upon long-term infusions in patients with impaired renal function. (See PRECAUTIONS, DOSAGE AND ADMINISTRATION).

Hepatic Impairment:

In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for dexmedetomidine were lower than in healthy subjects. The mean clearance values for subjects with mild, moderate, and severe hepatic impairment were 74%, 64% and 53% of those observed in the normal healthy subjects, respectively. Mean clearances for free drug were 59%, 51% and 32% of those observed in the normal healthy subjects, respectively.

Although Precedex is dosed to effect, it may be necessary to consider dose reduction in patients with hepatic impairment (see PRECAUTIONS, Hepatic Impairment and DOSAGE AND ADMINISTRATION).

Clinical Trials:

The safety and efficacy of Precedex has been evaluated in two randomized, double-blind, parallel-group, placebo-controlled multicenter clinical trials in 754 patients being treated in a surgical intensive care unit (ICU). All patients were initially intubated and received mechanical ventilation. These trials evaluated the sedative properties of dexmedetomidine by comparing the amount of rescue medication (midazolam in one trial and propofol in the second) required to achieve a specified level of sedation (using the standardized Ramsay sedation scale) between Precedex and placebo from onset of treatment to extubation or to a total treatment duration of 24 hours. The Ramsay Level of Sedation Scale is displayed in Table 2.

Table 2: Ramsay Level of Sedation Scale

Clinical Score	Level of Sedation Achieved
6	Asleep, no response
5	Asleep, sluggish response to light glabellar tap or loud auditory stimulus
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
3	Patient responds to commands
2	Patient cooperative, oriented, and tranquil
1	Patient anxious, agitated, or restless

In the first study, 175 patients were randomized to receive placebo and 178 to receive dexmedetomidine by intravenous infusion at a dose of 0.4 mcg/kg/hr (with allowed adjustment between 0.2 and 0.7 mcg/kg/hr) following an initial loading infusion of 1 (one) mcg/kg IV over 10 minutes. The study drug infusion rate was adjusted to maintain a Ramsay sedation score of ≥ 3. Patients were allowed to receive "rescue" midazolam as needed to augment the study drug infusion. In addition, morphine sulfate was administered for pain as needed. The primary outcome measure for this study was the total amount of rescue medication (midazolam) needed to maintain sedation as specified while intubated. Patients randomized to placebo received significantly more midazolam than patients randomized to dexmedetomidine (see Table 3).

A second prospective primary analysis assessed the sedative effects of dexmedetomidine by comparing the percentage of patients who achieved a Ramsay sedation score of ≥ 3 during intubation without the use of additional rescue medication. A significantly greater percentage of patients in the dexmedetomidine group maintained a Ramsay sedation score of ≥ 3 without receiving any midazolam rescue compared to the placebo group (see Table 3).

Table 3: Midazolam use as rescue medication during intubation (ITT)

	Study One		
	Placebo	Dexmedetomidine	p-value
	N=175	N=178	
Mean total dose (mg)of midazolam	19 mg	5 mg	0.0011*
Standard deviation	53 mg	19 mg	
Categorized midazolam use			
0 mg	43 (25%)	108 (61%)	<0.001**

0-4 mg	34 (19%)	36 (20%)
>4 mg	98 (56%)	34 (19%)

ITT (intent-to-treat) population includes all randomized patients.
*ANOVA model with treatment center. **Chi-square

A prospective secondary analysis assessed the dose of morphine sulfate administered to patients in the dexmedetomidine and placebo groups. On average, dexmedetomidine-treated patients received less morphine sulfate for pain than placebo-treated patients (0.47 versus 0.83 mg/h). In addition, 44% (79 of 178 patients) of dexmedetomidine patients received no morphine sulfate for pain versus 19% (33 of 175 patients) in the placebo group.

In a second study, 198 patients were randomized to receive placebo and 203 to receive dexmedetomidine by intravenous infusion at a dose of 0.4 mcg/kg/hr (with allowed adjustment between 0.2 and 0.7 mcg/kg/hr) following an initial loading infusion of 1 (one) mcg/kg IV over 10 minutes. The study drug infusion was adjusted to maintain a Ramsay sedation score of ≥ 3. Patients were allowed to receive "rescue" propofol as needed to augment the study drug infusion. In addition, morphine sulfate was administered as needed for pain. The primary outcome measure for this study was the total amount of rescue medication (propofol) needed to maintain sedation as specified while intubated.

Patients randomized to placebo received significantly more propofol than patients randomized to dexmedetomidine (see Table 4).

A significantly greater percentage of patients in the dexmedetomidine group compared to the placebo group maintained a Ramsay sedation score of ≥3 without receiving any propofol rescue (see Table 4).

Table 4: Propofol use as rescue medication during intubation (ITT) Study Two

	Placebo N=198	Dexmedetomidine N=203	p-value
Mean total dose (mg) of propofol Standard deviation	513 mg 782 mg	72 mg 249 mg	<0.0001*
Categorized propofol use			
0 mg	47 (24%)	122 (60%)	<0.001**
0-50 mg	30 (15%)	43 (21%)	
>50 mg	121 (61%)	38 (19%)	

*ANOVA model with treatment center. **Chi-square

A prospective secondary analysis assessed the dose of morphine sulfate administered to patients in the dexmedetomidine and placebo groups. On average, dexmedetomidine-treated patients received less morphine sulfate for pain than placebo-treated patients (0.43 versus 0.89 mg/h). In addition, 41% (83 of 203 patients) of dexmedetomidine patients received no morphine sulfate for pain versus 15% (30 of 198 patients) in the placebo group.

INDICATIONS AND USAGE

Precedex is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Precedex should be administered by continuous infusion not to exceed 24 hours.

WARNINGS

Precedex should be administered only by persons skilled in the management of patients in the intensive care setting. Due to the known pharmacological effects of Precedex, patients should be continuously monitored while receiving Precedex.

Clinically significant episodes of bradycardia and sinus arrest have been associated with Precedex administration in young, healthy volunteers with high vagal tone or with different routes of administration including rapid intravenous or bolus administration.

PRECAUTIONS

General:

Some patients receiving Precedex have been observed to be arousable and alert when stimulated. This alone should not be considered an evidence of lack of efficacy in the absence of other clinical signs and symptoms.

Reports of hypotension and bradycardia have been associated with Precedex infusion. If medical intervention is required, treatment may include decreasing or stopping the infusion of Precedex, increasing the rate of IV fluid administration, elevation of the lower extremities, and use of pressor agents. Because Precedex has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anticholinergic agents (e.g., atropine) should be considered to modify vagal tone. In clinical trials, atropine or glycopyrrolate were effective in the treatment of most episodes of Precedex-induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required.

Caution should be exercised when administering Precedex to patients with advanced heart block and/or severe ventricular dysfunction. Because Precedex decreases sympathetic nervous system activity, hypotension and/or bradycardia may be expected to be more pronounced in hypovolemic patients and in those with diabetes mellitus or chronic hypertension and in the elderly.

In situations where other vasodilators or negative chronotropic agents are administered, co-administration of Precedex could have an additive pharmacodynamic effect and should be administered with caution.

Transient hypertension has been observed primarily during the loading dose in association with the initial peripheral vasoconstrictive effects of Precedex. Treatment of the transient hypertension has generally not been necessary, although reduction of the loading infusion rate may be desirable.

Precedex infusion should not be co-administered through the same IV catheter with blood or plasma because physical compatibility has not been established. Safety and effectiveness of dexmedetomidine have not been evaluated in infusions over 24 hours. Dexmedetomidine is not indicated for infusions lasting over 24 hours (see INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION).

Withdrawal

Although not specifically studied, if Precedex is administered chronically and stopped abruptly, withdrawal symptoms similar to those reported for another alpha-2-adrenergic agent, clonidine, may result. These symptoms include nervousness, agitation, and headaches, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. Precedex should not be administered for greater than 24 hours (see INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION).

Adrenal Insufficiency

Dexmedetomidine had no effect on ACTH-stimulated cortisol release in dogs after a single dose; however, after the subcutaneous infusion of dexmedetomidine for one week, the cortisol response to ACTH was diminished by approximately 40%.

Hepatic Impairment

Since dexmedetomidine clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function (see CLINICAL PHARMACOLOGY, Pharmacokinetics, DOSAGE AND ADMINISTRATION).

Drug Interactions

General

In vitro studies in human liver microsomes demonstrated no evidence of cytochrome P450 mediated drug interactions that are likely to be of clinical relevance.

Anesthetics/Sedatives/Hypnotics/Opioids

Co-administration of Precedex with anesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with Precedex, a reduction in dosage of Precedex on the concomitant anesthetic, sedative, hypnotic or opioid may be required.

Neuromuscular Blockers

In one study of 10 healthy volunteers, administration of Precedex for 45 minutes at a plasma concentration of 1 (one) ng/mL resulted in no clinically meaningful increases in the magnitude of neuromuscular blockade associated with rocuronium administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal carcinogenicity studies have not been performed with dexmedetomidine.

Dexmedetomidine was not mutagenic *in vitro*, in either the bacterial reverse mutation assay *(E. coli* and *Salmonella typhimurium)* or the mammalian cell forward mutation assay (mouse lymphoma).

Dexmedetomidine was clastogenic in the *in vitro* human lymphocyte chromosome aberration test with, but not without, metabolic activation. Dexmedetomidine was also clastogenic in the *in vivo* mouse micronucleus test.

Fertility in male or female rats was not affected after daily subcutaneous injections at doses up to 54 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m2 basis). Dexmedetomidine was dosed from 10 weeks prior to mating in males and 3 weeks prior to mating and during mating in females.

Pregnancy: Teratogenic Effects. *Pregnancy Category C*

Teratogenic effects were not observed following administration of dexmedetomidine at subcutaneous doses up to 200 mcg/kg in rats from day 5 to day 16 of gestation and intravenous doses up to 96 mcg/kg in rabbits from day 6 to day 18 of gestation. The dose in rats is approximately 2 times the maximum recommended human intravenous dose on a mcg/m2 basis. The exposure in rabbits is approximately equal to that in humans at the maximum recommended intravenous dose based on plasma area-under-the-curve values. However, fetal toxicity, as evidenced by increased postimplantation losses and reduced live pups, was observed in rats at subcutaneous dose of 200 mcg/kg. The no-effect dose was 20 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m2 basis). In another reproductive study when dexmedetomidine was administered subcutaneously to pregnant rats from gestation day 16 through nursing, it caused lower pup weights at 8 and 32 mcg/kg as well as fetal and embryocidal toxicity of second generation offspring at a dose of 32 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m^2 basis). Dexmedetomidine also produced delayed motor development in pups at a dose of 32 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m2 basis). No such effects were observed at a dose of 2 mcg/kg (less than the maximum recommended intravenous dose on a mcg/m^2 basis).

Placental transfer of dexmedetomidine was observed when radiolabeled dexmedetomidine was administered subcutaneously to pregnant rats.

There are no adequate and well-controlled studies in pregnant women. Dexmedetomidine should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Labor and Delivery:

The safety of Precedex during labor and delivery has not been studied. Therefore, Precedex is not recommended during labor and delivery including cesarean section deliveries.

Nursing Mothers:

It is not known whether Precedex is excreted in human milk. Radiolabeled dexmedetomidine administered subcutaneously to lactating female rats was excreted in milk. Because many drugs are excreted in human milk, caution should be exercised when Precedex is administered to a nursing woman.

Pediatrics:

There have been no clinical studies to establish the safety and efficacy of Precedex in pediatric patients below 18 years of age. Therefore, Precedex is not recommended for use in this population.

Geriatrics:

A total of 531 subjects in the clinical studies were 65 years of age and over. A total of 129 subjects in the clinical studies were 75 years of age and over. In patients greater than 65 years of age, a higher incidence of bradycardia and hypotension was observed following administration of Precedex. Therefore a dose reduction may be considered in patients over 65 years of age.

Dexmedetomidine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in elderly patients, and it may be useful to monitor renal function.

ADVERSE REACTIONS

Adverse event information is derived from the placebo-controlled, continuous infusion trials of dexmedetomidine for sedation in the ICU setting in which 387 patients received Precedex. Overall, the most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever, vomiting, hypoxia, tachycardia and anemia (see Table 5).

Table 5: Treatment-Emergent Adverse Events Occurring in >1% of All Dexmedetomidine-Treated Patients in the Randomized Placebo-controlled Continuous Infusion ICU Sedation Studies		
Adverse Event	Randomized Dexmedetomidine (N=387)	Placebo (N=379)
Hypotension	28%	13%
Hypertension	16%	18%
Nausea	11%	9%
Bradycardia	7%	3%
Fever	5%	4%
Vomiting	4%	6%
Atrial Fibrillation	4%	3%
Hypoxia	4%	4%
Tachycardia	3%	5%
Hemorrhage	3%	4%
Anemia	3%	2%
Dry Mouth	3%	2%
Rigors	2%	3%
Agitation	2%	3%
Hyperpyrexia	2%	3%
Pain	2%	2%
Hyperglycemia	2%	2%
Acidosis	2%	2%
Pleural Effusion	2%	1%
Oliguria	2%	<1%
Thirst	2%	<1%

The treatment-emergent adverse events in Table 6 were reported in ≤1% of all dexmedetomidine-treated patients that are potentially clinically relevant.

Table 6: Potentially Clinically Relevant Treatment-Emergent Adverse Events to Dexmedetomidine Reported in ≤1% of Patients in the Continuous Infusion ICU Sedation Trials	
Body System	**Preferred Term**
Body as a Whole	Fever, Hyperpyrexia, Hypovolemia, Light Anesthesia, Pain, Rigors
Cardiovascular Disorders, General	Blood pressure fluctuation, Heart disorder, Aggravated hypertension
Central and Peripheral Nervous System Disorders	Dizziness, Headache, Neuralgia,Neuritis, Speech disorder
Gastrointestinal System Disorders	Abdominal pain, Diarrhea, Vomiting
Heart Rate and Rhythm Disorders	Arrhythmia, Ventricular arrhythmia, AV block, Cardiac arrest, Extrasystoles, Atrial fibrillation, Heart block, T wave inversion, Tachycardia, Supraventricular tachycardia, Ventricular tachycardia
Liver and Biliary System Disorders	Increased GGT, Increased SGOT, Increased SGPT
Metabolic and Nutritional Disorders	Acidosis, Respiratory acidosis, Hyperkalemia, Increased alkaline phosphatase, Thirst
Psychiatric Disorders	Agitation, Confusion, Delirium, Hallucination, Illusion, Somnolence
Red Blood Cell Disorders	Anemia
Respiratory System Disorders	Apnea, Bronchospasm, Dyspnea, Hypercapnia, Hypoventilation, Hypoxia, Pulmonary congestion
Skin and Appendages Disorders	Increased sweating
Vision Disorders	Photopsia, Abnormal vision

DRUG ABUSE AND DEPENDENCE

Precedex (dexmedetomidine hydrochloride) is not a controlled substance.

The dependence potential of dexmedetomidine has not been studied in humans. However, since studies in rodents and primates have demonstrated that dexmedetomidine exhibits pharmacologic actions similar to those of clonidine, it is possible that Precedex may produce a clonidine-like withdrawal syndrome upon abrupt discontinuation (see PRECAUTIONS, Withdrawal).

OVERDOSAGE

The tolerability of Precedex was noted in one study in which healthy subjects were administered doses at and above the recommended dose of 0.2 to 0.7 mcg/kg/hr. The maximum blood concentration achieved in this study was approximately 13 times the upper boundary of the therapeutic range. The most notable effects observed in two subjects who achieved the highest doses were first degree AV block and second degree heart block. No hemodynamic compromise was noted with the AV block and the heart block resolved spontaneously within one minute.

Five patients received an overdose of Precedex in the ICU sedation studies. Two of these patients had no symptoms reported; one patient received a 2 mcg/kg loading dose over 10 minutes (twice the recommended loading dose) and one patient received a maintenance infusion of 0.8 mcg/kg/hr. Two other patients who received a 2 mcg/kg loading dose over 10 minutes, experienced bradycardia and/or hypotension. One patient who received a loading bolus dose of undiluted Precedex (19.4 mcg/kg), had cardiac arrest from which he was successfully resuscitated.

DOSAGE AND ADMINISTRATION

Precedex should be administered using a controlled infusion device.

Precedex dosing should be individualized and titrated to the desired clinical effect. For adult patients, Precedex is generally initiated with a loading infusion of 1 (one) mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr. The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation. **Dexmedetomidine is not indicated for infusions lasting longer than 24 hours.**

Precedex has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue Precedex prior to extubation provided the infusion does not exceed 24 hours.

Dosage Adjustment

Dosage reductions may need to be considered for patients with renal impairment and hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS, Hepatic Impairment).

Dilution Prior to Administration

Precedex must be diluted in 0.9% sodium chloride solution prior to administration.

Preparation of solutions is the same, whether for the loading dose or maintenance infusion.

To prepare the infusion, withdraw 2 mL of Precedex and add to 48 mL of 0.9% sodium chloride injection to a total of 50 mL. Shake gently to mix well.

Administration With Other Fluids

Compatibility of Precedex with co-administration of blood, serum, or plasma has not been established. Precedex has been shown to be compatible when administered with the following intravenous fluids and drugs:

Lactated Ringers

5% dextrose in water, 0.9% sodium chloride in water, 20% mannitol, thiopental sodium, etomidate, vecuronium bromide, pancuronium bromide, succinylcholine, atracurium besylate, mivacurium chloride, glycopyrrolate bromide, phenylephrine HCl, atropine sulfate, midazolam, morphine sulfate, fentanyl citrate and a plasma-substitute.

Handling Procedures

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Strict aseptic technique must always be maintained during handling of Precedex. Vials are intended for single use only.

Compatibility studies have demonstrated the potential for absorption of dexmedetomidine to some types of natural rubber. Although Precedex is dosed to effect, it is advisable to use administration components made with synthetic or coated natural rubber gaskets.

Precedex must be diluted in 0.9% sodium chloride solution to achieve the required concentrations prior to administration. Preparation of solutions is the same, whether for the loading dose or maintenance infusion (see DOSAGE AND ADMINISTRATION).

HOW SUPPLIED

Precedex (dexmedetomidine hydrochloride injection), 100 mcg/mL as the base is available in 2 mL clear glass vial.

List No.	Container	Size
1638	Vial	2 mL

Store at controlled room temperature, 25°C (77°F) with excursions allowed from 15 to 30°C (59 to 86°F).

Manufactured and Distributed by:
Abbott Laboratories
North Chicago, IL 60064, USA

Licensed from:
Orion Corporation
Espoo, Finland

Printed in USA
Rev. Nov, 2000
ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA